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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/016,869	01/30/1998	DAVID H. BEACH	GPCI-P10-071	7533

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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	36

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/016,869	Applicant(s) BEACH ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,58,61-64,66,68-70,72-76 and 83-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,58,61-64,66,68-70,72-76 and 83-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 2/28/02 (Paper No. 33), is acknowledged.
Claims 59-60, 65, 67, 71, 77 and 79-82 have been cancelled.
Claims 1-10, 12-57 and 78 have been cancelled previously.
Claims 83-90 have been added.
Claims 11, 58, 61, 66 and 68-69 have been amended.

Claims 11, 58, 61-64, 66, 68-70, 72-76 and 83-90 are pending and are under consideration in the instant application.

2. The following is noted regarding the pending claims:
Claims 62 and 63 were listed as "Reiterated" in the amendment filed 2/28/02, but that the language of the claims had been amended.

Since claims 62 and 63 were listed as "Reiterated", they were not entered. If Applicant intends to amend claims 62 and 63, a new amendment is required.

In addition, it was noted after reviewing Applicant's Response filed 2/28/02 that the version of claim 68 examined in the Office Action mailed 11/21/01 was not the pending version of claim 68.

In view of this discrepancy, the several amendments of record, and the issues noted supra with respect to claims 62 and 63:

Applicant is requested to cancel all pending claims and introduce in their place a clean claim set in order to clearly establish which claim version is pending.

3. The revised Sequence Listing, CRF and Statement that the CRF and Sequence Listing are the same, filed 2/28/02 have been found acceptable.

The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. This Office Action will be in response to applicant's arguments, filed 2/28/02 (Paper No. 33).
The rejections of record can be found in the previous Office Action (Paper No. 32).

It is noted that New Grounds of Rejection are set forth herein.

5. Applicant's cancellation of claims 59-60, 65, 67, 71, 77 and 79-82 has obviated the previous objections and rejections with respect to these claims.

6. Any rejection or objection of record in Paper No. 32 not reiterated herein is withdrawn or obviated.

7. The Title stands objected to for failing to clearly indicate the invention to which the claims are directed.

Applicant should restrict the title to the claimed invention; i.e., antibodies to the cell cycle regulatory protein p16.

8. The specification stands objected to under 37 CFR 1.821(d) because SEQ ID NOS are not disclosed in the specification adjacent referenced sequences (for example, sequences appear on pages 32-33 of the instant specification that appear to corresponds to SEQ ID NOS:15-17, but that lack identifiers).

Although Applicant has stated in the Response filed 2/28/02 that the same sequences are provided sequence identifiers where the first appear on page 9 of the specification; the requirements of 37 CFR 1.8321(d) do not exempt same sequences appearing elsewhere in the specification. It is noted that in order to clearly establish that an application is in compliance with the Sequence Rules, each time a sequence is disclosed in the specification it must be accompanied by the appropriate sequence identifier.

Appropriate correction is required.

9. Claim 64 and newly added claim 86 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. A "labeled" antibody is broader in scope than the isolated antibody of the independent claim.

Applicant asserts in the Response filed 2/28/02 that the antibody of claim 58 (and newly added claim 83) can be either label or unlabeled, and that claim 64 therefore does further limit claim 58.

However, the specification does not appear to support that "antibody" encompasses both labeled and unlabeled antibodies as asserted (see e.g., specification page 33, 3rd full paragraph). In the absence of such a broad definition, a labeled antibody is broader in scope than the isolated antibody of claim 58.

It is suggested that Applicant re-write the claims in independent form.

10. Claim 68 is objected to because of the following informalities: it appears that "p16 kD" in the second line should be -- 16 kD --, as recited in the other claims.

11. Claims 76 and 90 are objected to because of the following informalities: it appears the last phrase of each claim was intended to read -- in samples *of* cells -- rather than "in samples *in* cells". Appropriate correction is required.

12. Claims 68, 70, 87 and 88 are objected to because of the following informalities: an article appears to be missing before the word "means". In claims 68 and 87 it appears the claims should read -- (ii) *a* means for detecting -- , while in claims 70 and 88 it appears the claims should each read -- wherein *the* means --.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. The previous rejection of claims 64, 68-70 and 72-76 under 35 U.S.C. 112, first paragraph, *New Matter* is withdrawn in view of Applicant's amendment filed 2/28/02 introducing adequate written description for a "labeled antibody" (claims 64, 69 and newly added claim 86) and a "kit comprising an isolated anti-CCR antibody" (claims 68-70 and 72-76 and newly added claims 87-90) via an incorporation by reference to this subject matter from USSN 08/154,915

15. Applicant's amendment, filed 2/28/02, has obviated the previous rejection of claims 11, 58, 61-64, 66, 68-70 and 72-76 under 35 U.S.C. 112, first paragraph, scope of enablement.

16. Claims 83-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody to a p16 protein *comprising* SEQ ID NO:35, does not reasonably provide enablement for an antibody to a p16 protein "having an amino acid sequence of" SEQ ID NO:35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. Applicant has disclosed only p16 comprising SEQ ID NO:35 or SEQ ID NO:2 (SEQ ID NO:35 with an additional 8 amino acids at the amino terminus) and antibodies to p16 proteins comprising SEQ ID NO:35 or SEQ ID NO:2. However, the instant claims encompass in their breadth an antibody that specifically reacts with any "p16 protein" having *any* "subsequence" of SEQ ID NO:35 by virtue of the recitation of a p16 protein "*having an amino acid sequence*" of SEQ ID NO:35. The breadth of the instant claims is therefore extensive.

The skilled artisan was well aware that many proteins can be characterized as "p16", and that most of these proteins would comprise a subsequence (have an amino acid sequence) of SEQ ID NO:35, particularly since there is no length requirement and the subsequence may be a small as a single amino acid. The skilled artisan was also well aware that antibodies to such proteins would share little if any functional activity with antibodies to p16 proteins *comprising the* amino acid sequence of SEQ ID NO:35. Therefore the skilled artisan would not reasonably expect that antibodies to these "p16" proteins "having an amino acid sequence of" SEQ ID NO:35 would function for detecting a cell cycle regulatory protein. Applicant has provided a working example only of antibodies to fusion proteins *comprising the* amino acid sequence of SEQ ID NO:35.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Since there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use either antibodies to "p16" proteins comprising subsequences of SEQ ID NO:35 or kits comprising such antibodies; the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

17. In claims 11, 58, 61-64, 66, 68-70 and 72-76, it is apparent that the WI38 cell line is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

In the instant case, it is noted that the WI38 cell line is available from the ATCC (CRL-75), and that there are no restrictions placed upon its availability to the public. Therefore, the Examiner considers the enablement requirement under 35 USC 112, first paragraph with respect to deposited material to be fulfilled.

18. Claims 83-90 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following written description rejection is set forth herein.

The instant claims are drawn to a genus of antibodies that specifically react with any "p16 protein" having *any* "subsequence" of SEQ ID NO:35 by virtue of the recitation of a p16 protein *"having an amino acid sequence"* of SEQ ID NO:35; as well as kits comprising these antibodies. However, this genus encompasses antibodies to any protein characterized as "p16" (i.e., having a molecular weight of approximately 16 kD by any assay) and comprising any subsequence of SEQ ID NO:35, even a subsequence as small as a single amino acid.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant has described only p16 proteins *comprising* SEQ ID NO:35. The genus of p16 proteins having an amino acid sequence of SEQ ID NO:35 is very large, and the genus of antibodies which specifically react these proteins even larger. There does not appear to be any disclosure of a known correlation between structure and function that must be shared by p16 protein having an amino acid sequence of SEQ ID NO:35, thus no correlation can be established for antibodies to such proteins.

Consequently, the claimed invention is not described in such a way as to reasonably convey to one of ordinary skill in the art that the inventor, at the time the application was filed, had possession of the invention. See Regents of the University of California v. Eli Lilly & Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Applicant is also directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Alternatively, Applicant should amend the claim to eliminate the subsequence language, e.g., by reciting "a p16 protein *comprising the* amino acid sequence of SEQ ID NO:35".

19. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 11, 58, 61-64, 66, 68-70 and 72-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 11, 58, 61-64, 66, 68-70 and 72-76 are ambiguous in their recitation of "a 16 kD protein" without an indication of the method and conditions used to assign the molecular weight. Apparent molecular weight varies depending upon the assay used to determine it and whether the protein is in a native or denatured form (e.g., the variable affecting several common methods of estimating molecular weight are reviewed in "Proteins: Structure and Molecular Properties, 2nd edition, Section 1.5, pages 23-28, by T.E. Creighton, W. H. Freeman and Company, 1993). Thus when a molecular weight is recited as a protein characteristic, the claims must also include the method by which it was determined (e.g. PAGE, gel filtration, etc.) and the conditions used (e.g., reducing, denaturing, etc.) in order to avoid ambiguity.

B) Claims 62 and 63 are indefinite in that each is dependent on canceled claims 59 and 60. Claims 62 and 63 should be amended to depend only from a pending claim.

C) Claims 72-76 are ambiguous in their recitation of "wherein the antibody" because claim 68, from which these claims depend either directly or indirectly, recites both an anti-CCR antibody and an anti-CDK4 antibody.

Applicant should amend the dependent claims to clearly indicate the intended antibody.

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

21. The following is noted with respect to the effective filing date of the instant claims:

Applicant provided in the response filed 2/28/02 a copy of priority document USSN 07/991,997.
A copy of USSN 08/154,915 was previously provided on 10/25/00 by Applicant.
USSN 08/227,371 was not available to the Examiner.
As noted previously, USSN 08/248,812 appears to provide the same support as the instant application; thus all claims appear to be entitled to at least a priority date of 5/25/94.

The right of priority to earlier USSNs of the instant claims is summarized below:

	'869 (instant)	'915 (11/18/93)	'997 (12/17/92)
antibodies to "p16"	page 33	page 27	not found
Fab	page 33	not found	not found
F(ab')2	page 33	not found	not found
monoclonal Ab	page 33	page 27	page 7
purified polyclonal Ab	page 33	not found	not found
antisera	page 33	page 27	page
p16 antibody kit	incorporated	page 28	not found
labeled p16 antibody	incorporated	page 29	not found
16kD protein co-IP with CDK4 in Wi38	page 52-53	page 25	pages 29-30, Fig 2

The Examiner was unable to identify written support for purified polyclonal antibodies and antibody fragments, including Fab and F(ab')2 fragments, in either the '915 or '997 applications. *Thus the priority date of instant claims 62-63 and 74-75 (reciting fragments), and of 66 and 73 (reciting preparation of polyclonal antibodies) appears to be at least 5/25/94, but not 11/18/93.*

The Examiner was also unable to identify clear support for an antibody to the p16 protein in priority document USSN 07/991,997. Although antibodies to the p16-CDK4 complex are contemplated in USSN 07/991,997 (e.g., page 7), the '997 application does not appear to provide adequate written support for an antibody "specifically reactive with" the p16 protein. *Thus the priority date of claims 11, 58, 61, 64, 68-70, 72, 76 and 83-90 appears to be the same as that of USSN 08/154,915, i.e., 11/18/93.*

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

23. Claims 66 and 73 are rejected under 35 U.S.C. 102(e) as being anticipated by Kamb (US Pat No. 6,090,578, of record, see entire document).

Kamb teaches and claims an antibody which binds a mammalian MTS1 polypeptide (see entire document, including claims). Kamb also teaches that the MTS1 polypeptide and p16 are the same protein (see entire document; e.g. column 16, especially lines 53-65; column 38, especially lines 51-67; and SEQ ID NO:2 of Kamb). Kamb teaches that the p16/MTS1 protein is a cell cycle regulatory protein that binds the cyclin-dependent kinase CDK4 (see columns 43-45, especially column 44 at lines 13-35). Kamb teaches that the anti-MTS1/p16 antibodies may be polyclonal, monoclonal, or antibody fragments (e.g., columns 14-15 and 55-56). Kamb also teaches that the purified antibodies may be labeled with a detectable label (e.g., column 15 at lines 24-40 and column 27-28). In addition, Kamb teaches diagnostic kits for detecting the MTS1/p16 cell cycle regulatory protein comprising antibodies to the p16/MTS1 cell cycle regulatory protein (e.g. columns 27-28 in view of columns 15 and 55-56).

Therefore the teachings of the reference anticipate the instant invention.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of antibodies to a p16/MST1 protein. It is noted that p16/MST1 is inherently a 16 kD protein that coprecipitates with CDK4 from lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody.

While Applicant has argued in the Response filed 2/28/02 that the instant claims are entitled to a priority date that precedes that availability date of the reference, this argument has not been found convincing with respect to claims 66 and 73 for the reasons set forth supra under the analysis of priority.

24. Claims 66 and 73 are rejected under 35 U.S.C. 102(e) as being anticipated by Skolnick et al. (US Pat No. 5,624,819, of record; see entire document).

Skolnick et al. an antibody which binds a mammalian MTS1 polypeptide (see entire document). Skolnick et al. also teach that the MTS1 polypeptide and p16 are the same protein (see entire document; e.g. column 16, especially lines 43-54; column 38, especially lines 1-16; and SEQ ID NO:2). Skolnick et al. teach that the p16/MTS1 protein is a cell cycle regulatory protein that binds the cyclin-dependent kinase CDK4 (see columns 43-44, especially column 43 at lines 9-50). Skolnick et al. teach that the anti-MTS1/p16 antibodies may be polyclonal, monoclonal, or antibody fragments (e.g., columns 14-15 and 54-55); and that the purified antibodies may be labeled with a detectable label (e.g., column 15 at lines 20-31 and column 27). In addition, Skolnick et al. teach diagnostic kits for detecting the MTS1/p16 cell cycle regulatory protein comprising antibodies to the p16/MTS1 cell cycle regulatory protein (e.g., column 27 in view of columns 15 and 54-55).

Therefore the teachings of the reference anticipate the instant invention.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of antibodies to a p16/MST1 protein. It is noted that p16/MST1 is inherently a 16 kD protein that coprecipitates with CDK4 from lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody.

While Applicant has argued in the Response filed 2/28/02 that the instant claims are entitled to a priority date that precedes that availability date of the reference, this argument has not been found convincing with respect to claims 66 and 73 for the reasons set forth supra under the analysis of priority.

25. The previous rejection of claims 68-70, 72-73 and 76 under 35 U.S.C. 102(b) as being anticipated by Busch et al. (US Pat No. 4,794,077, of record) is withdrawn. It is noted that claim 68 was in fact limited by an amendment filed 5/29/01 to require that the antibody react with a p16, which is clearly not anticipated by the 145kD protein of Busch et al.

26. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

27. Claims 11, 58, 61-64, 66, 68-70, 72-76 and 83-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xiong et al. (Genes & Dev. August 1993; 7:1572-1583, IDS #EO) in view of Busch et al. (US Pat No. 4,794,077, of record).

Applicant's arguments, filed 2/28/02, have been fully considered but have not been found convincing.

Applicant provides a copy of priority document USSN 07/991,997 and argues that in view of the '997 application the Xiong et al. reference is antedated.

However, although Applicant points to page 7 at lines 14-18 of USSN 07/991,997 and asserts that this disclosure provides adequate support for p16 isolation, purification, and antibodies; as noted supra this disclosure appears to be in reference only to antibodies to the p16-CDK4 *complex*. Therefore, there does not appear to be adequate written support for antibodies to p16 or antibodies to a 16 kD protein that coprecipitates with CDK4 from lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody.

Consequently, the Xiong et al. reference published in August 1993 is available as prior art under 35 USC 102(a) with respect to all pending claims, since it was published less than a year before the effective filing dates of 11/18/93 (claims 11, 58, 61, 64, 68-70, 72, 76 and 83-90) and 5/25/94 (claims 62-63, 66 and 73-75).

In addition, although a reference that is not a statutory bar under 35 USC 102(b) may be antedated, in order to antedate a reference a proper Declaration under 37 CFR 1.131 (or 37 CFR 1.132, if appropriate) must be filed (MPEP 7.15.01(d).

Therefore, Xiong et al. is available as a reference under 35 USC 102(a) at this time.

The rejection of record in Paper No. 32 is reiterated below as applied to the instantly pending claims:

The claims are drawn to antibodies, antibody preparations and kits comprising antibodies to a 16 kD protein that coprecipitates with CDK4 from lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody.

Xiong et al. teach a p16 cell cycle regulatory protein that is 16 kD and that binds to and coprecipitates with the cyclin-dependent kinase CDK4 from cell lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody (see entire document, especially Figure 1). Xiong et al. teach that the molecular identity of p16 was unknown, but that it associates with proteins involved in cell cycle progression that are altered in oncogenically transformed cells, and that studies addressing possible altered responses involving cell cycle regulatory proteins are important to understanding oncogenesis (e.g., see "Discussion"). Xiong et al. purify p16 from several human cellular sources, including the WI38 cell line transformed with SV40 (the VA13 cell line, see "Cell Culture" on page 1581) and provide a peptide map to show that p16 is the same in each case (e.g., Figure 6). Xiong et al. also teach the production of antibodies to other proteins involved in cell cycle regulation (see entire document, especially "Antibodies and Immunological Methods" on page 1581), and use these antibodies to study the association and expression of various cell cycle proteins (see entire document).

Xiong et al. do not teach an antibody, antibody preparation, or kit comprising an antibody to a 16 kD protein that coprecipitates with CDK4 from lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody, nor an antibody to p16.

Busch et al. teach and claim a kit comprising an antibody to a cell cycle regulatory protein (p145) and a detectable label for detecting the antibody (see entire document, especially claims 3-15 and column 11). Means for detecting the cell cycle regulatory protein are taught that include both a detectable label conjugated to the antibody (e.g. column 11 at lines 15-26 and claim 16) and a second antibody (e.g., column 11 at lines 27-41). Both monoclonal and purified polyclonal antibody preparations are taught (see entire document, especially claims 3-5 and 14-15). Busch et al. teach throughout the reference that the antibodies are formulated for detecting the protein in samples of cells (e.g., columns 7-8).

Given the teachings of the references, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare antibodies, antibody preparations, and kits comprising antibodies to the p16 taught by Xiong et al. Given the teachings of Xiong et al. that p16 is associated with CDK4 and involved in cell cycle progression and possibly the mechanism underlying oncogenesis, one of ordinary skill in the art would have been motivated to provide an antibody, antibody preparation, or kit comprising an antibody to p16 in order to study p16's role in cell cycle and oncogenesis. As taught by both Xiong et al. and Busch et al., one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of successfully producing antibodies to p16 and formulating them in various diagnostic kits for detecting p16 in a sample of cells. Although the amino acid sequence of p16 is not taught by either reference, the sequence in an intrinsic property of the protein and thus a recitation of sequence composition does not render an antibody to the protein unobvious. Finally, although Fab and $F(ab')_2$ fragments are not taught explicitly by either reference, these forms of antibodies were well known to one of ordinary skill in the art at the time the invention was made. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

28. Claims 62-63 and 74-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over either
Kamb (US Pat No. 6,090,578, of record), or
Skolnick et al. (US Pat No. 5,624,819, of record)
in view of Owens et al. (J. Immunol. Methods February 1994; 168:149-165.

The claims are drawn to Fab and $F(ab')_2$ fragments of an antibody to a 16 kD protein that coprecipitates with CDK4 from lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody, as well as kits comprising these antibody fragments.

Both Kamb and Skolnick et al. have been discussed supra.

Although both Kamb and Skolnick et al. teach antibody fragments specifically reactive with a 16 kD protein that coprecipitates with CDK4 from lysate of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody, as well as kits comprising antibody fragments; neither Kamb or Skolnick et al. exemplify Fab and $F(ab')_2$ fragments of the antibodies they teach.

Owens et al. teach that it was well known in the art that antibody fragments were the reagent of choice for some clinical applications (see entire document, but especially comment on page 149, 2nd paragraph). Owens et al. also teach that Fab and $F(ab')_2$ fragments are the fragments typically produced, and have been invaluable as diagnostic reagents (e.g., page 155, 2nd column).

In view of the art-recognized applicability of Fab and $F(ab')_2$ fragments for both in vitro and in vivo diagnostic applications, as taught by Owens et al.; it would have been obvious to the ordinary artisan at the time the invention was made to formulate the antibody fragments taught by either Kamb or Skolnick et al. as Fab and $F(ab')_2$ fragments. The ordinary artisan would have been motivated to select Fab and $F(ab')_2$ fragments as the antibody fragments produced in view of the established utility of Fab and $F(ab')_2$ fragments in diagnostic applications, as taught by Owens et al. Given that the techniques for producing Fab and $F(ab')_2$ fragments were well established at the time the invention was made, the ordinary artisan would have had a reasonable expectation of successfully producing Fab and $F(ab')_2$ fragments. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

29. No claim is allowed.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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